

Articles

Deep Brain Stimulation for Tremor Associated with Underlying Ataxia Syndromes: A Case Series and Discussion of Issues

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Abstract

Background: Deep brain stimulation (DBS) has been utilized to treat various symptoms in patients suffering from movement disorders such as Parkinson's disease, dystonia, and essential tremor. Though ataxia syndromes have not been formally or frequently addressed with DBS, there are patients with ataxia and associated medication refractory tremor or dystonia who may potentially benefit from therapy.

Methods: A retrospective database review was performed, searching for cases of ataxia where tremor and/or dystonia were addressed by utilizing DBS at the University of Florida Center for Movement Disorders and Neurorestoration between 2008 and 2011. Five patients were found who had DBS implantation to address either medication refractory tremor or dystonia. The patient's underlying diagnoses included spinocerebellar ataxia type 2 (SCA2), fragile X associated tremor ataxia syndrome (FXTAS), a case of idiopathic ataxia (ataxia not otherwise specified [NOS]), spinocerebellar ataxia type 17 (SCA17), and a senataxin mutation (SETX).

Results: DBS improved medication refractory tremor in the SCA2 and the ataxia NOS patients. The outcome for the FXTAS patient was poor. DBS improved dystonia in the SCA17 and SETX patients, although dystonia did not improve in the lower extremities of the SCA17 patient. All patients reported a transient gait dysfunction postoperatively, and there were no reports of improvement in ataxia-related symptoms.

Discussion: DBS may be an option to treat tremor, inclusive of dystonic tremor in patients with underlying ataxia; however, gait and other symptoms may possibly be worsened.

Keywords: Tremor, SCA2, SCA17, fragile X syndrome, myoclonic dystonia, deep brain stimulation, unilateral

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Introduction

Though deep brain stimulation (DBS) has been utilized as a treatment for a variety of neurological and neuropsychiatric disorders, ataxia syndromes have been rarely addressed.¹⁻⁵ There are specific

symptoms other than the ataxia that may possibly be treated through the use of DBS. Most prominently, these symptoms include medication refractory tremor and dystonia. We present a series of five such

Table 1. Pre- and Postoperative Validated Rating Scales for the Ataxia DBS Cases

| Subject | Scale | Preop Score | 6 Months Post DBS | 12 Months Post DBS |
|-------------------|------------|-------------|-------------------|--------------------|
| SCA2 | TRS: motor | 51 | DBS on: 31 | DBS on: 26 |
| | | | DBS off: 35 | DBS off: 33 |
| FXTAS | TRS: motor | 60 | DBS on: 57 | DBS on: 45 |
| | | | DBS off: 60 | DBS off: 62 |
| Ataxia NOS | TRS: motor | 40 | DBS on: 27 | N/A |
| | | | DBS off: 29 | N/A |
| SCA17 | BFMDRS | 15 | DBS off 32 | DBS on 17 |
| SETX | UDRS | 34 | DBS on: 34 | DBS on: 38 |
| | | | DBS off: 35 | |

Ataxia NOS, Ataxia Not Otherwise Specified; BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale; DBS, Deep Brain Stimulation; FXTAS, Fragile X Ataxia Syndrome; SCA2, Spinocerebellar Ataxia Type 2; SCA17, Spinocerebellar Ataxia Type 17; SETX, Senataxin Mutation-associated Ataxia; TRS, Tremor Rating Scale; UDRS, Unified Dystonia Rating Scale.

patients where tremor, or alternatively dystonia in the setting of an ataxia syndrome was addressed by utilizing DBS.

To date, there are few available reports of the effects of DBS on patients with ataxia.^{1,6–10} Mostly, these cases highlight improvement of symptoms via stimulation, although side effects were not always detailed. There are several reports of successful treatment of dystonia with DBS in pantothenate kinase-associated neurodegeneration (PKAN),⁷ which is also a syndrome that may result in ataxia symptoms. The remaining published studies focused on tremor suppression with thalamic and/or subthalamic stimulation in spinocerebellar ataxia type 2 (SCA2),^{1,8} spinocerebellar degeneration (SCD),⁹ and fragile X tremor ataxia syndrome (FXTAS).^{6,10–13} There have not been previous reports of DBS for spinocerebellar ataxia type 17 (SCA17)-related dystonia or in DBS for a senataxin mutation-related dystonia. We will discuss the pre- and postoperative course of thalamic ventralis intermedius nucleus (Vim) DBS that was employed for tremor cases associated with SCA2, FXTAS, and an idiopathic, young-onset ataxia where no genetic mutation was uncovered (ataxia not otherwise specified [NOS]). We will also report the outcome of dystonia treated with globus pallidus interna (GPi) DBS in a case of SCA17 and in a single case of a senataxin (SETX) mutation.

Methods

A retrospective Institutional Review Board-approved database review (UF-INFORM) of all DBS patients operated on at the Center for Movement Disorders & Neurorestoration at the University of Florida from 2008 to 2011 was performed. We screened cases for the presence of an ataxia syndrome, and included only patients without another primary neurological or neuropsychiatric diagnosis (Parkinson's disease, dystonia, essential tremor, Huntington's disease, obsessive compulsive disorder, and Tourette's syndrome).

The potential risks and benefits of DBS were discussed at length with each patient, prior to surgical intervention. Each patient underwent risk stratification by the University of Florida Center for Movement Disorders and Neurorestoration Interdisciplinary DBS team. This risk stratification involved an evaluation by movement disorders neurology, neurosurgery, neuropsychology, psychiatry, physical therapy, occupational therapy, and speech/swallow therapy.

Microelectrode recording was performed without anesthesia in an attempt to identify and map the corresponding target (Vim or GPi). Macrostimulation was performed to confirm thresholds for benefits and side effects and a 3387 DBS lead (Medtronic, Minneapolis, MN) was implanted. The placement of the ventral electrode tip was confirmed postoperatively by computed tomography (CT)–magnetic resonance imaging (MRI) fusion. A second DBS lead was placed stereotactically, 2 mm anterior to the first lead, on a single case (FXTAS). One month following lead implantation, subclavicular generators (Soletta, Medtronic) were implanted under general anesthesia and connected to the DBS leads. The stimulators were activated 30 days following the initial surgery, and stimulation-induced thresholds were checked for side effects and benefits at each contact on the DBS lead. Empirical programming in the clinic occurred on average, once a month for 6 months, so that the most effective clinical settings could be identified for chronic treatment. Pre–post rating scale scores are summarized in Table 1 and postoperative DBS lead locations (ventral tip) derived from CT–MRI fusion are summarized in Table 2. Programming parameters are summarized in Table 3.

Case reports

Case 1: SCA2

A 41-year-old right-handed Caucasian female of Cuban decent presented with tremor in her hands. She had been asymptomatic until

Table 2. Postoperative Lead Locations for Ataxia DBS Patients

| Subject | Target | Right | Left |
|-------------------|--------|-------------------------|--------------------------|
| SCA2 | Vim | | X 11.2, Y -6.4, Z -1.9 |
| FXTAS | Vim | | X -12.9, Y -9.9, Z -0.79 |
| | VOA | | X -13.4, Y -7.89, Z -1.7 |
| Ataxia NOS | Vim | | X -13, Y -6.91, Z -3.5 |
| SCA17 | GPI | X 18, Y 1.8, Z -4.1 | X -20.5, Y 1.8, Z -6.6 |
| SETX | GPI | X 19.5, Y 0.71, Z -4.57 | X -22, Y -0.3, Z -4.2 |

Lead locations were derived from computed tomography–magnetic resonance imaging fusion. Measurements were made in reference to the mid-commissural point: Y, anteroposterior; X, mediolateral; Z, axial; Vim, Thalamic Ventralis Intermedius Nucleus; GPI, Posteroventral Globus Pallidus Internus; VOA–VOP, Thalamic Ventralis Oralis Anterior and Ventralis Oralis Posterior. Ataxia NOS, Ataxia Not Otherwise Specified; FXTAS, Fragile X Ataxia Syndrome; SCA2, Spinocerebellar Ataxia Type 2; SCA17, Spinocerebellar Ataxia Type 17; SETX, Senataxin Mutation-associated Ataxia.

age 27 and, over the course of many years, she developed a gait ataxia, which required the use of a wheelchair by age 41. Coincident with the gait decline was a decrement in speech and swallowing function. In the 2 years prior to her presentation, she had developed difficulty with handwriting, signing her name, and in her activities of daily living (such as eating) due to her tremor and also her ataxia. On neurological examination, she had a very mild dysmetria, and a clumsiness in her upper extremities as well as a moderate truncal and gait ataxia. There were slow saccadic movements on horizontal gaze, and her deep tendon reflexes were diminished. Her tremor was limited to her upper extremities, and was more distal than proximal. The tremor was present with rest and posture, but most pronounced with action. She had mild bradykinesia, but no rigidity. She underwent genetic testing, which revealed 44 CAG repeats on the ATXN gene, which confirmed the diagnosis of SCA2.

She was treated with maximally tolerated dosages of primidone 250 mg and levetiracetam 3000 mg, which failed to suppress her tremor. Botulinum toxin injections (total 235 units) in her forearm decreased tremor, but resulted in intolerable muscular weakness. Given her poor response to treatment, she elected to have a left Vim DBS in an attempt to suppress her right-hand tremor and to improve her activities of daily living, including her eating and her handwriting. After surgery, she reported improvements from the implantation effects alone with resolution of her resting tremor, and improvement of both postural and action tremor of her right arm. However, her gait worsened following the surgery, and she required inpatient rehabilitation for 2 weeks to restore her gait to her preoperative baseline. At her 12-month follow-up visits, her Fahn–Tolosa–Marín Tremor Rating Scale (TRS) scores had markedly improved compared with baseline. Her ataxia did not change. She did not elect to undergo a contralateral

Table 3. Deep Brain Stimulation Programming Settings for Ataxia Cohort

| Subject | Target | Cathode(s) (–) | Anode (+) | Voltage (V) | Pulse Width (μ s) | Frequency (Hz) | Postop Month |
|-------------------|-----------|-------------------|--------------|----------------|---------------------------|-------------------|-----------------|
| SCA2 | Left Vim | 2 | C | 1.8 | 90 | 135 | 12 |
| FXTAS | Left VOA | 2 | C | 3.3 | 120 | 135 | 12 |
| | Left Vim | 6 | C | 3.3 | 150 | 135 | |
| Ataxia NOS | Left Vim | 0 | 2 | 3.2 | 180 | 135 | 6 |
| SCA17 | Left GPI | 1 | 3 | 3.2 | 450 | 185 | 12 |
| | Right GPI | 1 | 3 | 3.2 | 450 | 185 | |
| SETX | Left GPI | 1 | C | 4.6 | 180 | 100 | 12 |
| | right GPI | 1, 2 | C | 3.6 | 150 | 100 | |

Ataxia NOS, Ataxia Not Otherwise Specified; FXTAS, Fragile X Ataxia Syndrome; GPI, Globus Pallidus Interna; SCA2, Spinocerebellar Ataxia Type 2; SCA17, Spinocerebellar Ataxia Type 17; SETX, Senataxin Mutation-associated Ataxia; Vim, Ventralis Intermedius Nucleus; VOA, Ventralis Oralis Anterior.

DBS, citing satisfaction with tremor control, and also a fear of risking gait deterioration.

Case 2: FXTAS

A 72-year-old male presented with tremor that was interfering with his activities of daily living. At the time of his visit, he required caregiver assistance to dress, shave, and to eat. His difficulties began 15 years prior, and he initially reported he had a minor intention tremor of the right hand, which slowly progressed to include his head and later his body. He eventually developed balance impairment, a wide-based gait, and he reported generalized clumsiness. His family history was significant for tremor in his mother, and in his brother, who had similar symptoms. He had a normal cognitive examination. His baseline TRS motor score was 60. He had severe tremor of both upper extremities with posture and intention. His postural tremor and intention tremors were worse than his resting tremor. The tremor prohibited him from completing all of the writing portions of the examination. His cerebellar examination revealed dysmetria and dysdiadochokinesis. He had a cerebellar rebound phenomenon in both upper extremities, and past pointing when performing the finger chase maneuver. He could not perform tandem walking, but was able to walk unassisted, though it was unsteady. Polyneuropathy was present, with moderate proprioceptive problems, and he had mild pain and temperature loss (more in the toes, and ankles but also present in his fingers). His reflexes were diminished in his arms and legs, and his ankle jerks were absent. A formal diagnosis of FXTAS was made through the use of genetic testing, which revealed a pre-mutation in the FMR1 gene with 100 CGG trinucleotide repeats.

He was treated with primidone 250 mg and propranolol 20 mg and he had a very mild benefit, which quickly waned. He was successfully treated with botulinum toxin A to address his head tremor. His severe arm tremor and his inability to perform his activities of daily living led to him to considering DBS therapy. After placement of the first lead at the Vim–VOP border, there was mild tremor suppression in the resting tremor and postural tremor, but there remained severe intentional tremor. A second lead was then placed in the same sitting at the VOP–VOA border and, intraoperatively, there was a near complete tremor suppression, and only a mild residual ataxia. He underwent monthly visits for reprogramming, and despite multiple setting changes he did not make functional improvements in the tremor without experiencing intolerable side effects of stimulation including unsteady gait. His family stated his tremor was mildly improved. Postoperatively at 6 months, his TRS scores remained similar to his preoperative scores; however, he felt he had some improvement of his postural and truncal tremors.

Case 3: Ataxia NOS

A 40-year-old male was referred for evaluation of ataxia, dystonia, and tremor. At the age of 12 years he developed head tremor, along with bilateral hand tremor. The syndrome gradually progressed to include a writer's cramp, bilateral foot inversion, ataxia, and gait instability. His activities of daily living were progressively compromised, and he noted

that his most significant problem was difficulty when attempting to eat independently. His neurological examination was significant for poor proprioception and vibratory sense in his feet bilaterally, as well as generalized depression of his deep tendon reflexes, with absent ankle jerks, and the presence of Babinski signs bilaterally. He previously underwent a genetic work-up for his tremor and ataxia which included SCA1, 2, 3, 6, 7, 8, 10, and Dentatorubral-pallidoluysian atrophy (DRPLA), and all testing was normal. He was diagnosed with an idiopathic tremor–ataxia syndrome (ataxia NOS). He was previously treated with clonazepam and propranolol with only minor benefits, and levodopa was not helpful. Given the tremor component of his syndrome, and the effect on his activities of daily living, he elected to undergo a left Vim DBS implantation.

Intraoperatively, there was successful suppression of the resting tremor, postural tremor, and intentional tremor; however, there remained a significant ataxic component to his movements. Postoperatively, he described himself as “much improved” despite only mild improvements in his overall functional status. There were modest improvements on his postoperative TRS scales at 6 months after surgery. He stated he had a worsening of his gait with stimulation, but that he could adjust his settings on an as-needed basis, and that he was able to utilize higher settings while eating and lower settings while walking. He had no worsening of gait, and he observed no change in the degree of ataxia in his upper extremities.

Case 4: SCA17

A 37-year-old right-handed Caucasian male without a family history of movement disorders presented with a slowly progressive gait disturbance over the course of 20 years. His first symptoms of gait difficulty began at age 12. At age 15, he developed generalized dystonia, with a severe inversion of his left foot. This progressed to include a twisting of his neck and shoulders that was worsened by action. He also developed a postural-action tremor in both of his arms. His symptoms gradually worsened, and by the time of his presentation at our clinic, he suffered from marked dystonic posturing of his face, shoulders, neck, and legs all contributing to gait difficulty. He also had a moderate, proximal more than distal postural and intention tremor. This tremor presented bilaterally, and was dystonic in character. His general neurological examination was otherwise unremarkable, and he had no clinical signs of gait ataxia.

He was initially diagnosed with a generalized dystonia and trials of maximally tolerated dosages of levodopa, trihexyphenidyl, baclofen, and botulinum toxin injections failed to improve his symptoms. Given his poor response to medication, and marked dystonia, he underwent staged bilateral GPi DBS surgery to improve the foot dystonia. One month after his initial DBS programming, he noted dramatic improvements in his upper extremity dystonic tremor; however, there was no improvement noted in his lower extremity dystonia. He reported that his fall frequency of five or six times a day was unchanged by DBS implantation. Multiple DBS programming adjustments did not improve his gait. The “Off” DBS condition revealed a re-emergence of upper extremity dystonic tremor. Three

months postoperatively he developed an ataxic wide-based quality to his gait, and his fall frequency increased. This was present whether on or off DBS. He also observed new slurring of his speech, and his neurological examination revealed mild dysarthria, bilateral dysmetria, and severe gait ataxia without saccadic or ocular pursuit abnormalities. There was significant gait and stance ataxia, and mild appendicular ataxia. He was able to stand only with assistance, and he began using a power scooter. His dystonia scales continued to worsen at his 12-month follow-up and multiple DBS settings were attempted without dystonia and ataxia benefit. He was, however, able to maintain tremor benefit. He had negative genetic testing results for DYT1, and for SCAs 1, 2, 3, 6, 7, 8, 10, and Dentatorubral-pallidolysian atrophy (DRPLA). His molecular genetic testing for SCA17, however, demonstrated an expanded allele of 43 repeats, and a normal allele of 32 CAA/CAG repeats in the TATA-binding protein gene.

Case 5: *senataxin* mutation

A 19-year-old right-handed male was referred for ataxia and myoclonic jerking of his extremities. His symptoms began in infancy with hypotonia and multiple delayed motor milestones. He began talking at an appropriate age, but his speech was described as slurred from a very early age. At age 2, his mother reported that his arms and his head were held in an abnormal posture, and that he had titubation of his body when walking. During his school years, he required personal aides in the classroom setting because of his tremor and jerking, both of which interfered with his normal activities. His tremor had become disabling over the past 5 years, and he utilized a straw to drink because of his inability to hold a cup. His neurological examination revealed limited horizontal gaze in both directions, though his oculocephalics were normal. His horizontal saccades were slow, but without nystagmus. He had a cerebellar rebound phenomenon bilaterally, and he had prominent dysmetria on finger-to-nose, and heel-to-shin testing. His gait was wide based with dystonic inward posturing of his feet, which was worse on his left side. His hands were dystonic bilaterally. There was a bilateral upper extremity tremor, and it was both resting and postural, and the tremor had an irregular frequency. Fast myoclonic jerks were observed in both upper extremities at rest, and with action, more in the left than right upper extremity. His family reported that his neurological condition was slowly worsening and was definitely progressive over many years. His previous work-up included a gene test for SCA1, 2, 3, 6, 7, 8, and 10, all of which were within normal range. Brain MRI, electroencephalogram, and an electrocardiogram were all normal. Wilson's disease and Niemann-Pick disease work-ups were negative and a skin biopsy for electron microscopy was negative. However, an amino acid change was found on codon 992 (lysine to arginine) on the *SETX* gene, and he was diagnosed with a *senataxin*-associated myoclonus, dystonia, and tremor syndrome. He declined testing for the myoclonus dystonia gene because of financial constraints.

Multiple medications were titrated to maximally tolerated dosages in an attempt to treat his dystonia, tremor, and myoclonus, and these included primidone, valproic acid, clonazepam, acetazolamide,

levodopa, buspirone, and levetiracetam. The propranolol 30 mg and gabapentin 1200 mg could mildly suppress his tremor, and he remained on these medications at the time of presentation. He elected to undergo staged bilateral GPi DBS surgery with the goal of improving the dystonic posturing and tremor in his hands, and to attempt to improve eating and handwriting.

Postoperatively, he had improvement in his dystonic tremor and an almost complete resolution of his myoclonus, although overall his Unified Dystonia Rating Scale (UDRS) was not improved. After his second GPi DBS was placed, he reported some transient worsening of his gait, which he said slowly returned to baseline preoperative levels. He was satisfied with his functional improvement, despite the lack of objective improvements on his UDRS. His handwriting was better, and he could hold a pen and he could type as a result of the DBS. He was able to eat and drink without spilling, which was a personal preoperative goal. He rated himself as much improved.

Discussion

In each of the five ataxia patients receiving DBS therapy, all reported postoperative improvements in tremor. However, dystonia did not improve in two patients. The cases were all associated with some level of postoperative gait impairment.

Rhythmic postural and action tremor in ataxia patients seemed to respond to Vim DBS in a similar way to what has been observed in essential tremor; however, the ataxia, clumsiness, and gait dysfunction did not respond. In our cohort, the SCA2 patient had the greatest amount of tremor suppression, and she reported ipsilateral as well as contralateral benefit. The Ataxia NOS patient also had excellent tremor suppression. In contrast, the FXTAS patient had a dramatic intraoperative improvement in his tremor, but the improvement was not sustained, even with the addition of a second DBS lead into the VOA/VOP region. Interestingly in the SCA2 and ataxia NOS patients, the TRS markedly improved in the off-DBS setting when compared with baseline, but minimally improved in the on-DBS condition, which contrasted to the FXTAS patient where improvement in the TRS score was only seen after turning the DBS on. This contrast in outcomes could possibly have been due to differences in the degree of the microlesion (i.e. implantation) effect. The single case reports in the literature on DBS in ataxia patients highlight the potential, and also the shortcomings to applying this therapeutic approach to a complex and heterogeneous population.^{1,6,8–13} Whether the ataxia can worsen due to DBS remains controversial, and though gait worsened it is important to recognize that gait and balance may also worsen following Vim DBS for essential tremor.¹⁴ A staged Vim DBS procedure has been reported to worsen ataxia following a second lead implantation in a FXTAS case.¹¹ Therefore, collectively one might conclude that caution should be exercised, and that a preoperative risk-benefit ratio discussed prior to considering bilateral procedures in patients with ataxia.

Dystonic tremor responded to GPi DBS in SCA17 and in the *senataxin* mutation cases and this contrasted to the response seen in dystonia. GPi DBS has been reported to improve dystonic tremor as well as dystonia;¹⁵ however, the results for dystonia in the setting of

ataxia were not as robust as has been reported in primary generalized and in cervical dystonia.

Although our case series included heterogeneous cases and a small number of cases, the results demonstrated the potential benefits and also the side effects of DBS surgery in patients with ataxia syndromes. Additionally, the discrepancy between subjective and objective improvement in our cases may possibly indicate the shortcomings of traditional objective rating scales that may not capture mild improvements. Quality of life and other measures should be included in future ataxia DBS studies. It is likely that a subset of carefully selected patients may benefit from DBS, though the outcomes will likely be less robust than in essential tremor and in primary dystonia. The unilateral procedures in our small case series resulted in side effects and this issue should be kept in mind by treating clinicians who may opt for a staged approach with interval and careful clinical evaluation before proceeding to implant a contralateral DBS lead. Each ataxia DBS candidate should be counseled preoperatively about potential gait issues, and also should be counseled that DBS will be unlikely to benefit the ataxic components of their disease.

In conclusion, DBS may be an option to treat tremor, including dystonic tremor in patients with underlying ataxia; however, gait and other symptoms may be worsened. Whether choosing unilateral, staged bilateral, or simultaneous bilateral DBS implantation(s) for ataxia syndromes, a careful preoperative risk benefit discussion should be pursued with patients and families.

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